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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/856,327	06/07/2001	Yoshimitsu Takakura	0230-0157P	6836

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EXAMINER	
SNEDDEN, SHERIDAN	
ART UNIT	PAPER NUMBER
1653	12

DATE MAILED: 11/05/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/856,327	TAKAKURA ET AL.	
	Examiner	Art Unit	
	Sheridan K Snedden	1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-27* is/are pending in the application.

4a) Of the above claim(s) *1-10,21 and 25-27* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *11-20 and 22-24* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *20 September 2000* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *11* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

1. Applicant's election of invention II, claims 11-18 and 22-24 is acknowledged. Claims 1-10, 19-20 and 25-27 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **with** traverse in Paper No. 10.

2. Applicant argues that the restriction requirement was only considered under 35 USC 121 and overlooks PCT Rule 13. Applicant argues that the inventions share a common special technical feature of the antimicrobial protein of Group I. This argument is non-persuasive. PCT Rule 13.2 states that unity of invention referred to in Rule 13.1 shall be fulfilled only when there is a technical relationship among those inventions involving one or more of the same or corresponding special technical features. Annex B, Part 1(b), indicates that "special technical features" means those technical features which as a whole define a contribution over the prior art. A special technical feature of a protein with antimicrobial pyranose oxidase activity is not a contribution over the prior art as it is taught by Nishimura *et al.*. Thus the invention of Groups I-IV lack unity of invention.

3. After further consideration, Groups II and III are rejoined as both represent sequences as part of the gene of SEQ ID NO: 1. Claims 11-20 and 22-24 are pending.

Specification

4. The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed. See for example, "Antimicrobial protein from *Lyophyllum shimeji*."

Drawings

5. The Draftsman has approved drawing sheets 1-2 submitted on June 7, 2001.

Claim Rejections - 35 USC § 101

6. 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 11-18 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. As stated, the claims recite a gene of natural origin and does not show the hand of man. Applicant is advised to include the words "isolated" or "purified" in the recitation of the invention directed towards protein to indicate the hand of man.

Claim Rejections - 35 USC § 112

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 11-20 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one

skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Applicant is also referred to the Guidelines on Written Description published at FR 66(4) 1099-1111 (January 5, 2001) (also available at www.uspto.gov).

Claims 11-18 are directed in part to a nucleic acid sequence that encodes an antimicrobial protein comprising at least 50% sequence similarity with SEQ ID NO: 1 or substitutions, deletions, insertions or additions thereof. The specification discloses the nucleic acid sequence as SEQ ID NO: 1 and concepts regarding the meaning of "percent" (%) (page 11); however, there is no description of the differences brought about by a percent similarity difference (e.q., if there is a similarity difference of 73, 86 or 92%) that would result in a biologically active protein. Applicants may wish to amend the claims to delete the references to '% homology,' and to indicate a specific, measurable function. See specification wherein the function of the encoded protein is stated to be an antimicrobial. Similarly, claim 12 is directed to a gene that contains substitutions, deletions, insertions and/or additions but fails to indicate a specific, measurable function. There is no apparent discussion of what part(s) the polynucleotide would have to remain, or would have to be added, such that the antimicrobial function or the encoded protein was retained.

Claims 19 and 20 are directed to oligonucleotides for obtaining the gene, comprising at least 50% homology to SEQ ID NO 1, encoding an antimicrobial protein. Claims 19 and 20 also recite option modifications to these oligonucleotides. However, there is no apparent discussion of what part(s) the oligonucleotide would have to remain, or would have to be added, such that gene encoding an antimicrobial protein was obtained.

9. Claim(s) 11-18 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for nucleic acid molecule of SEQ ID NO: 1 encoding an antimicrobial protein, does not reasonably provide enablement for a gene sharing 50%-95% sequence identity with SEQ ID NO: 1 encoding an antimicrobial protein. The specification does not enable a person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims. As currently stated, the invention would include nucleic acid sequences of 50-95% identity to SEQ ID NO: 1.

In this regard, the application disclosure and claims have been compared per the factors indicated in the decision *In re Wands*, 8 USPQ2d 1400 (Fed. Cir., 1988) as to undue experimentation. The factors include:

1) the nature of the invention;
2) the breadth of the claims;
3) the predictability or unpredictability of the art
4) the amount of direction or guidance presented;
5) the presence or absence of working examples;
6) the quantity of experimentation necessary;
7) the state of the prior art; and,
8) the relative skill of those skilled in the art;

Each factor is addressed below on the basis of comparison of the disclosure, the claims and the state of the prior art in the assessment of undue experimentation.

1) the nature of the invention;

In the instant case, the invention is a gene encoding an antimicrobial protein that possesses 50-100 % sequence homology to SEQ ID NOs: 1. The only gene sequence expressly taught is that of SEQ ID NO: 1.

2) the breadth of the claims;

The invention would consist of all genes whose primary sequence shares a 50% to 100% sequence identity to that of SEQ ID NO: 1 and encodes an antimicrobial protein. As stated, the invention is drawn to thousands of gene sequences that would encode thousands of different amino acid sequences.

It cannot be predicted by one of skill in the art that nucleic acids that share at least 50% homology to the gene of SEQ ID NO: 1 will encode a protein with the same antimicrobial activity as the gene of SEQ ID NO: 1. Bowie et al (1990, Science 247:1306-10) teach that an amino acid sequence encodes a message that determines the shape and function of a protein and that it is the ability of the protein to fold into unique three-dimensional structures that allows it to function and carry out the instructions of the genome. The cited reference also teaches that the prediction of protein structure from sequence data and, in turn, utilizing predicted structural determinations to ascertain functional aspects of the protein, is extremely complex (pg 1306, left column). Bowie et al teach that while it is known that many amino acid substitutions are possible in any given protein, the positions within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of maintaining function are limited. Certain positions in the sequence are critical to the three-dimensional structure/function relationship, and these regions can tolerate only conservative substitutions or none at all (pg 1306, right column).

3) the predictability or unpredictability of the art;

The DNA and protein sequence arts are recognized as unpredictable, as minor changes in the nucleotide or amino acid sequences to these molecules may produce profound changes in biological activity. The physiological structure and function of a protein cannot be determined based solely on sequence identity to the primary sequence of the gene of SEQ ID NO: 1.

The sensitivity of proteins to alterations in even a single amino acid in a sequence is exemplified by Lazar et al (1988, Mol. Cell. Biol. 8:1247-1252), who teach that a replacement of aspartic acid at position 47 with alanine or asparagine in transforming growth factor alpha had no effect, but that replacement with serine or glutamic acid sharply reduced biological activity (see the abstract). Thus, Lazar *et al.* demonstrated that one or few amino acid substitutions could dramatically affect the biological activity and the structure-function characteristics of a protein.

Indeed, a search of the prior art identified a nucleic acid molecule which shares a 53.5% sequence identity with the gene of SEQ ID NO: 1 (see SEQ IN NO: 2 of Kawamura *et al.*). The nucleic acid of Kawamura *et al.* codes for an antitumor protein as opposed to a protein showing antimicrobial activity. Thus, sequence homology does not lead to predictable function.

4) the amount of direction or guidance presented;

The specification discloses a protein that possesses antimicrobial activity, and particularly, possesses antimicrobial activity against *Rhizoctonia solani* and *Pyricularia oryzae*. The specification discloses the cDNA of the above protein.

The claims recite a gene, which contains both introns and exons, which are not adequately disclosed in the specification. No discussion is provided as to the number of introns and exons and to what sequences make up each exon and intron.

Additionally, as the claims recite % homology, the specification fails to indicate what regions or positions of the cDNA or protein are required in order for the protein to maintain antimicrobial activity and thus, leads to greater unpredictability of outcome for predicting function based on % homology.

5) the presence or absence of working examples;

The specification provides examples of a 65 and 70 kDa protein comprising the amino acid sequences of SEQ ID No: 3-6. These proteins possessed a pyranose oxidase activity. The specification provides examples of how the cDNA encoding the above protein was identified.

The specification does not provide examples of what regions, domains or sequences that are required for the protein to maintain the antimicrobial activity. As minor changes in the nucleotide or amino acid sequences may produce profound changes in biological activity (see Lazar *et al.* above), direction should be provided as to what is the minimal sequence necessary for the protein to maintain the antimicrobial activity.

6) the quantity of experimentation necessary;

Given the claim breath, unpredictability, and lack of guidance as discussed above, undue experimentation would have been required by one skilled in the art to develop and evaluate all nucleic acids with 50-100% identity to SEQ ID NO: 1 encoding proteins with antimicrobial activity. Making all possible substitutions, insertions and deletions in an nucleic acid molecule so that at least 50% sequence identity is maintained to SEQ ID NO: 1 would require making and analyzing an innumerable population of nucleic acids.

It is the specification, not the knowledge of one skill in the art that must supply the novel aspects of an invention in order to constitute adequate enablement. As it is not clear that a gene of at least 50% homology to SEQ ID NO: 1 will encode an antimicrobial protein, a person of ordinary skill in the art would not be able to identify all genes sharing at least 50% homology to SEQ ID NO: 1 and possessing antimicrobial activity without undue experimentation

7) the state of the prior art; and,

Included in the discussion of the predictability or unpredictability of the art (see factor 3).

8) the relative skill of those skilled in the art;

> It is concluded that a person skilled in the art would be unable to identify genes encoding antimicrobial proteins given the above discussion. To be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation. As such, a person skilled in the art is only taught how to identify the cDNA of SEQ ID NO: 1.

Given the claim breath, unpredictability in the art, undue experimentation, and lack of guidance in the specification as discussed above, the instant invention is not enabled throughout the full scope of the claims.

10. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 11-18 and 22-24 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 11 is rejected for being dependent on non-elected claims and should be rewritten in independent format.

In claim 19, line 5, the word 'form' should be replaced with 'form'.

Claim 19 and dependent claims thereto is indefinite because it is unclear as to what minimal sequence is required. As recited, the claim is directed to an oligonucleotide based on any domain of SEQID NO 1 that may be further modified.

Claims 12-18 and 22-24 are rejected for being dependent on indefinite claim 11.

Claim 12 is indefinite as to the meaning of "stringent conditions." The specification exemplifies 'stringent conditions' on page 16, lines 17-21, however the example is not considered definitive.

Claim 12 is indefinite as SEQ ID NO: 1 is a coding segment but claims 12 recites a sequence that would hybridize to SEQ ID NO: 1. That which hybridizes does not encode the same protein.

Claim 12 is written with "having (line 1) which, absent definition in the specification, is pen language and equivalent to "comprising". The remainder of the claims are written in alternative format and are considered in appropriate language for a Markush type claim. Please use appropriate closed "selected from the group consisting of" language.

Art of Record

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure: Nishimura *et al.* (US Patent 5,712,139).

Nishimura *et al.* teach a method of obtaining a pyranose oxidase gene using oligonucleotides. Nishimura *et al.* does not teach the gene of SEQ ID NO 1 or oligonucleotides complementary to the sequence. There would have been no motivation or predictability to use the oligonucleotides of Nishimura *et al.* to obtain a gene from Lyophyllum shimeji.

Advisory Information

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sheridan K Snedden whose telephone number is (703) 305-4843. The examiner can normally be reached on Monday - Friday, 8:30 AM to 5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low can be reached on (703) 308-2923. The fax phone numbers for the

organization where this application or proceeding is assigned are (703) 746-3975 for regular communications and (703) 746-3975 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

SKS
November 4, 2002

SKS

CHRISTOPHER S. F. LOW
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